Smith (G. M.)

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GOUVERNEUR M. SMITH, M.D.,

PHYSICIAN TO THE NEW YORK AND PRESBYTERIAN HOSPITALS.

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From Dr. G. M. S.

DERANGEMENT OF THE GLYCOGENIC FUNCTION OF THE LIVER AS A CAUSE OF BRIGHT'S DISEASE.

By GOUVERNEUR M. SMITH, M.D.,
PHYSICIAN TO THE NEW YORK AND PRESBYTERIAN HOSPITALS.

Investigations relating to the etiology of Bright's disease have, within a few years, been prosecuted with special care. Such investigations have proved of great practical utility. In the first place, they have enabled physicians, to a certain extent, to guard against the prevalence of a malady which is of frequent occurrence in this latitude, and which is dreaded on account of its mortal character. In the second place, such studies have enabled medical men to treat the disorder in a more satisfactory manner, and when patients have been relieved of their more distressing symptoms, and are able to resume the ordinary duties of life, they can often be placed under circumstances tending to prevent further injury to the renal texture.

The term Bright's disease is employed in such a manner that it includes diverse pathological conditions of the kidneys. Each structure entering into the composition of the renal emunctories is liable to morbid changes. Such changes may be confined primarily to one structure, other structures becoming subsequently involved, or there may be apparently a contemporaneous morbid eruption, involving all the tissues, the initial lesion escaping observation.

It is a well-recognized fact, as shown by post-mortem examinations, that very different diseased appearances of the kidneys are observed in the bodies of those succumbing from renal dropsy, and it is possible that the causes of these diverse conditions may have been as different as are the lesions which are discovered. At the same time, it must be admitted that combined causes may have been operative in producing complex lesions, and, again, diverse causes may be provocative of a like lesion.

It may seem unscientific to group together heterogeneous lesions and classify them under one disorder. In time, this group of morbid phenomena will be dissected into accurate subdivisions—each subdivision being as distinctly recognized by name as is the distinct nomenclature now employed to designate the group. No apology seems absolutely necessary, however, as yet, for the continued use of the term Bright's disease, which

has become so universally employed, for while it is often inferred under what kind of a renal lesion a patient is suffering, nevertheless in most forms of lesions of the kidneys, to which special allusion has been made, while there may be distinctive signs of each lesion, there is still, owing to the interruption of the renal functions, such an analogy of symptoms as to still warrant a generic term to express them.

The design of this article is to call attention to a special point in the etiology of renal dropsy, viz., *derangement of the glycogenic function of the liver as a cause of Bright's disease.* Now, in order to illustrate this subject, it appears to me desirable to review, in a brief manner, the causes of Bright's disease ordinarily recognized, and to review some points relating to hepatic sugar formation. In doing this I must be pardoned if reference is made to my former investigations on these subjects, which reference will partially explain how a novel cause of a renal malady has more recently been suggested to my mind.

In a paper read before the New York Academy of Medicine, April 1, 1869, and published in Volume III. of the Academy's *Transactions*, I endeavoured to illustrate the etiology of Bright's disease by an analysis of three hundred and eight cases of the disorder occurring in the New York Hospital. The limits of this article will not allow of a full review of all the points brought forward therein, it must suffice to allude to a few of them as introductory to the subjoined thoughts.

In regard to the causes of acute Bright's disease, or tubal nephritis as it has been denominated, the following causes were alluded to: exposure to cold and wet, and checking perspiration, sequel of measles, of scarlet fever, and of malarial fever, immoderate alcohol drinking, obstructions to the escape of bile, an irritable state of the urine as occurring in various diseases, and the internal administration of turpentine, cantharides, arsenic, etc.

Respecting the chronic form of Bright's disease in a considerable proportion of the two hundred and sixty-eight cases before alluded to, the causes were apparently assignable, and these may be enumerated as follows: intemperance, climatic exposures to the inclemencies of the weather, malarial poisoning, workings in lead, opium habit, gout and rheumatism, diseases of the heart, while a number of patients had suppurating sores.

Dickinson, in his admirable treatise on albuminuria, says:—

"The following are the conditions to which granular degeneration of the kidneys can be traced:—

"1st. Conditions which produce and maintain venous congestion of the kidney, such as valvular disease of the heart and pregnancy.

"2d. The gouty habit, from whatever circumstance it arise, but more especially when it is associated with lead.

"3d. A general tendency to fibroid degeneration, as shown by changes in the liver, lungs, and other organs.

"Further, it must be allowed that the disease arises in certain cases in consequence of a local tendency peculiar to the individual, or as a result of influences of which as yet we know nothing."

Concerning the amyloid kidney, or "depurative infiltration," as it has been denominated, it is constantly associated with cancerous, syphilitic, and tubercular diseases, and indeed with other disorders, accompanied by profuse suppuration, other viscera besides the kidneys being similarly and simultaneously affected.

At this stage, attention is particularly called to a special point. Dickinson has shown, in speaking of albuminuria, that "arctic cold and equatorial heat are equally inimical to its development. It chiefly abounds where the mean temperature of the year is not far removed from 50° F." My study of this subject as relating to this Continent, and as shown in the paper before alluded to, seemed to corroborate this opinion.

In comparing the mortuary tables of widely scattered localities in our section of the northern hemisphere, it was found that Bright's disease was most prevalent in regions where the seasons are most marked, and where the vicissitudes from heat to cold are often abrupt and intense. If such climatic causes can induce chronic congestion, and ultimately organic lesions in the kidneys, it can be legitimately inferred that other causes, which lower the tone of the system and which induce a pretty constantly diminished temperature of the body, can produce similar results.

Here a digression must be made, in order to fully understand the conclusions arrived at in this article.

After looking into the subject of Bright's disease, my attention was directed to that of diabetes, and in a paper on that disorder, read before the New York Academy of Medicine, Feb. 2d, 1871,[1] I took occasion to present some novel views regarding the uses of hepatic glycogenesis. Subsequently to this time, viz., on June 15th, 1871, Dr. Dalton read a paper before the Academy on sugar formation in the liver, and by request I took part in the discussion, and confined my remarks to the "Uses and Derangements of the Glycogenic Function of the Liver."[2]

The physiologists up to this period had directed their investigations strictly towards deciding the question whether or not the liver possessed a glycogenic function, and had not, so far as I am aware, made known any very specific uses for the function. It seemed to be proved by the experiments of Bernard, Flint, Lusk, and Dalton, that sugar was generated by the liver, and could readily be traced from this viscus to the right side of the heart; that the blood of the general circulation contained but a small quantity of sugar, but in the right side of the heart it occurred in a double or quadruple quantity as compared with that found in the jugular vein.

From these facts it appeared to me a legitimate inference that such a constant and normal hepatic glycogenesis must have a benign purpose in the economy, and, further, that, as a function, it must be as liable to derangement as are the other functions of the animal economy. The liver

[1] Transactions New York Academy of Medicine, vol. iii.

[2] Ibid., New Series, vol. i.

might generate the sugar either too freely or too sparsely, or might entirely fail to create it; or, again, an abnormal form of sugar might be elaborated, or some material which is not sugar, and which, though perhaps allied to it, is a diseased product, and fails to supply the economy with a material susceptible of being utilized in a healthful manner. An increased amount of sugar as occurring in the disorder known as diabetes had long been recognized and made an object of investigation; but respecting these other points no researches, so far as my observation extended, had been made.

A brief epitome of some of the views relating to these topics, which I have before offered on the occasion alluded to, may here be introduced as a further introduction to the subject under special consideration.

Sugar, as generated by the liver, can be traced to the right side of the heart and to the lungs. Now what disposition is made of this saccharine material in the pulmonary organs? In the lungs, the sugar may be largely destroyed and eliminated as carbonic acid and water, an *evolution of heat* attending the metamorphosis, and a partial explanation afforded respecting the maintenance of animal heat. An analogous process of vital chemistry is observed in young and growing plants, by which sugar is made subservient to the production of a suitable degree of temperature. The process, however, is not an identical one. Part of the sugar in vegetables, under the influences of bio-chemical transformations, is converted into permanent tissue; while another part is broken into its elements to form varied organic associations, and during these combinations and recombinations an evolution of heat occurs; thus affording a necessary and normal temperature to cotyledons, radicles, and plumules of the tiny embryo, and indeed to growing plants of maturer growth. Phyto-chemical processes are with difficulty observed, but under master minds have been interpreted. If we turn either to the most infinitesimal or to the most gigantic vegetable forms, we find them possessed with the power of maintaining a temperature adapted to the necessities of each; and in them starch, sugar, and oil play important roles as heat-producing factors. In the animal kingdom, both the insignificant and the potential forms of life are endowed with the power of maintaining a certain degree of temperature. Diverse as are the vegetable and animal creations, kindred proximate principles are operative in both, in the production of kindred results, though the processes of vital chemistry may not be alike in the two realms of nature.

Respecting the disposition of hepatic sugar in the economy, while a part of the saccharine material may be destroyed in the lungs and its elements eliminated, another part may be converted in the pulmonary organs into some other principle or principles which the physiologists have not recognized, and which, passing into the circulation, may either be chemically disposed of and eliminated, or be converted into tissues composed of carbon, hydrogen, and oxygen. As a result of these and of other chemi-

cal processes, warmth is generated—a warmth so tempered by the divine will, that a glow is maintained, genial and adapted to the different classes and species of animals.

There are good reasons for believing that hepatic glycogenesis is increased at times, both under normal and abnormal conditions. It appears to me it can account for *obesity*. In those individuals inclined to the accumulation of adipose tissue, the liver doubtless generates more sugar than ordinary, and it is disposed of in the economy by a conversion into fat. As corroborative of this, it may be stated that we not unfrequently notice a temporary glycosuria in stout persons. This variety of diabetes is not ordinarily fatal, and I account for the occurrence of the phenomenon in this manner: more sugar is occasionally formed than can be utilized in the system, and the surplus passes away in the renal secretion.

A normal augmented hepatic glycogenesis occurs, I think, during lactation; the irritation of the mammary glands, etc., at the close of gestation excites, by a nervous influence, increased sugar formation in the liver, the blood of the general circulation becomes charged with it, this sugar is separated from the blood by the mammary glands, and appears somewhat modified as lactose in the milk. In proof of this, it is known that milk is richer in sugar early in lactation than at later periods; and, again, nursing women and milch cows have been observed to have a temporary melituria.

These phenomena, relating to the quality of milk and to glycosuria in young mothers, which had been observed as clinical facts, had not, so far as I was aware, been explained, and I have, on a former occasion, accounted for them in this manner: mammary irritation early in lactation is more potent than at later seasons, and better calculated to excite reflex nervous influences; and, again, more sugar is generated than is required for the milk, and hence the appearance of the extra supply as an excretion in the urine. Patients suffering with confirmed diabetes have been observed to eliminate sugar in various secretions, as in the saliva and perspiration, as well as in pus.

It is a natural supposition, as a converse to the above, that sugar formation may be either arrested or diminished, and that symptoms indicative of such condition should be as conspicuous as are those which are indicative of an extraordinary quantity. Nature ordinarily may be so conservative as to diminish or increase the production of sugar to meet the demands of the system during the varying seasons of the year. In our latitude diabetes is a malady of rare occurrence; in certain warm regions it is a disorder so frequently met with that scarcely a family escapes its appearance. We recognize diverse causes as giving rise to the symptom of glycosuria. In tropical countries we are aware of the great prevalence of hepatic disorders, as provoked by a variety of circumstances, and it is probable that the hepatic sugar, not being all required to maintain animal temperature, is excreted in the renal secretion.

Among the patients constantly coming under our observation in this climate, cases are often observed in which the patients are lean and dyspeptic, and who suffer sensations of chilliness and have little endurance of cold. These phenomena are particularly noticeable among those suffering from functional and organic diseases of the liver; there is probably, in other words, a concomitant derangement of both the glycogenic and biliary functions. Sugar is not degenerated in quantities sufficient either to maintain animal heat or to be converted into fat. It is occasionally observed that lean persons have a normal temperature, and can withstand inclement surroundings. In such cases it is presumable that the saccharine material is utilized in the economy in the production of heat, and not in the production of adipose tissue. It sometimes happens that, when the production of sugar is excessive, as in melituria, the temperature of the patient is below the normal standard, the sugar being only partially turned to a profitable account, the great mass of it being eliminated.

The fact is well recognized that certain nervous conditions favour an abnormal increase in glycogenesis; it would seem to be likewise true that other nervous conditions occur which arrest or diminish sugar formation. As it would be beyond the limits of this paper to discuss at length these and other etiological points relating to these interesting phenomena, it must suffice to confine our attention to a single sequel of a diminished hepatic saccharine production. I shall have to omit a consideration of numerous noteworthy points relating to the question how far derangements of the glycogenic function directly or indirectly either cause or modify various acute or chronic diseases. Variations of the function modify vital processes, and induce both trivial and grave morbid *sequelæ*.

If, as we have before seen, certain climatic causes can induce in the kidneys organic disease, and if diminished sugar supply can induce a diminished animal temperature, it seems a legitimate conclusion that persons suffering under such saccharine impoverishment, and living in certain latitudes, are peculiarly liable to renal disease. The function may be so diminished that, without climatic causes, the system may be lowered in vitality, rendering the kidneys peculiarly liable to chronic congestion and organic lesion. A new factor of disease is thus found to be operative, and this factor, simultaneously operative with other morbid factors, induces diverse, complex, and widely diffused lesions. The more closely we study the relationships of organs and functions, the more readily can we understand their mutual dependencies, and the more clearly can we perceive how derangements in one or more can induce derangements in others.

The conclusions to be drawn from the foregoing pages may be epitomized as follows:—

First. Among the causes giving rise to one form of the disorder known as Bright's disease, climate is recognized as a potential one—climatic influences being chiefly operative in such sections of the earth where the

vicissitudes of the weather are sharp and abrupt, especially as occurring in localities of the temperate zone.

Second. One of the uses of the glycogenic function of the liver is to maintain animal temperature. The function in question may be deranged in various ways. Sugar may not be formed at all, or may be formed in unduly large quantities, or may be generated so sparsely as to be insufficient to subserve the wants of the economy. In a case where the sugar is suppressed, or is prepared in very moderate quantities, animal temperature is diminished, and the person suffers in a manner similar to that of one exposed to harsh atmospherical conditions, and is liable to chronic congestion and organic lesion of the kidneys; and if such an individual is a resident of a region in which the mean annual temperature is about 50° F., he is peculiarly prone to injury of the renal textures.

Third. Lessons in the prophylaxis of Bright's disease and the treatment of the disorder are derived from the above considerations. As means of prevention, care must be bestowed upon the nervous system, resort must be had to dietetic measures, extreme attention being paid towards promoting the healthy performance of the various functions, while the artificial temperature of apartments and personal protection by clothing when exposed to inclement vicissitudes are important measures of defence.

Patients already suffering under chronic Bright's disease are by no means irremediable, unless their cases are very seriously complicated. A large proportion of such cases leave our hospitals relieved, and with the prospect of future usefulness, if strict attention is paid to the salutary rules of treatment which can be enjoined. It has fallen to my lot to see in hospital, consultation, and private practice no inconsiderable amount of renal disease—especially of Bright's disease. It has been to me a matter of surprise how much can be accomplished by careful treatment in the relief of such patients. When such invalids have been relieved of the more urgent symptoms which confine them either to the bed, or to the room, or to the house, very much can be done by hygienic means to promote restoration to comparative health, even though there is an assurance that the kidneys have undergone organic changes and can never be reinstated to an absolutely normal condition.

In promoting recuperation, special care is taken to relieve the kidneys of all unnecessary work. The diet is particularly regulated, both as respects quality and quantity, so that only the essential requirements of food, suited to each case, shall be ingested. In health the kidneys are constantly overtasked in their duties by reason of the inconsiderate use as well of solid aliments as of beverages. I have come to regard a rigid dietetic regimen as being as essential to the restoration of patients suffering with granular degeneration of the kidneys, etc., as the restricted diet in the management of diabetes, although of course the modifications and restrictions

are not the same in the two disorders. No less attention is paid to the functions of the skin, and daily and general lavements and frictions are insisted upon in order to promote increased cutaneous exhalation and largely relieve the kidneys of duties ordinarily devolving upon them.

The temperature of apartments is made a matter of special regulation, and clothing suited to in-door and out-door life is prescribed. While under such hygienic measures, patients are further enjoined to take small doses of corrosive sublimate, under which treatment amelioration is generally manifest. Without any change of climate, patients may thus be placed under conditions rendering life not only comfortable, but also fitted to perform the ordinary duties incident to it.

It occasionally happens, however, that harsh and wintry surroundings are incompatible with such a degree of recuperation, and in advising the removal of a patient to a genial clime, we have to consider, in the words of Milton—

> "By what means to shun
> The inclement seasons, rain, ice, hail, and snow,
> Which now the sky, with various face, begins
> To show us, . . . while the winds
> Blow moist and keen, shattering the graceful locks
> Of these fair spreading trees; which bid us seek
> Some better shroud, some better warmth."

Postscript.—On the completion of the above paper, and when about mailing the manuscript for publication, an interesting and able article has fallen under my notice in the *American Journal of Science and Art*, Feb. 1878, by Dr. Joseph Le Conte, denominated "Some Thoughts on the Glycogenic Function of the Liver and its Relation to Vital Force and Vital Heat." It has been my aim to give the foregoing article a practical bearing; the length of the paper has forbidden the presentation of the various theories in regard to the precise manner by which sugar is formed as derived from the liver. Several questions relating to this subject are still *sub judice*, but physiologists agree that saccharine blood ordinarily flows from the liver, and without discussing mooted points regarding its source, I have endeavoured to show how derangements of such a flow can unfavourably affect the animal economy.

Dr. Le Conte, without alluding to the subject considered in this paper, has alluded to a connection between the hepatic and renal functions. He says:—

> "We have seen that albuminoids, whether food or waste tissues, are probably split in the liver into glycogen and some nitrogenous residuum. The glycogen is changed into sugar, and then by oxidation into CO_2 and H_2O, and eliminated by the lungs. The nitrogenous residuum, if it is not at first urea, is at least easily changed into urea and eliminated by the kidneys. We see then the *close relation* between the functions of the liver and kidneys."